Decision Memo for Liver Transplantation for Malignancies other than Hepatocellular Carcinoma (CAG-00101N)

Decision Summary

In summary, after studying the technology assessment report prepared by AHRQ, reviewing much of the literature independently and discussing the issue with noted leaders in the transplant community in the U.S., we find that:

(1) available evidence does not indicate that liver transplantation for malignancies other than HCC produces outcomes that are comparable to those achieved with other liver transplants;

(2) there are no cohort studies comparing liver transplantation to other treatment options for any non-HCC malignancy; and

(3) most of the available literature is individual case studies or very small case series and is not adequate to make a positive coverage determination.

Nonetheless, we evaluated the information provided in the studies and found that:

(1) the information suggests that liver transplantation for non-HCC malignancy produces outcomes statistics in terms of mortality that are substantially lower than transplantation for other diagnoses;

(2) the transplants do not appear to be curative in the majority of the cases since in over half of recipients the disease recurs;

(3) there has been a significant decline in the number of transplants performed for non-HCC malignant disease in the U.S.

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act. (Section 1869(f)(1)(B).) In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within part A or part B, and must not be otherwise excluded from coverage. (In this case, liver transplantation falls within the inpatient hospital and physician services benefit categories.) Moreover, in general, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. (section 1862(a)(1)(A).)

As described in this decision memorandum, we have fully examined the medical and scientific evidence submitted with the request for a national coverage decision. CMS determines that the evidence is not adequate to conclude that liver transplantation in patients with non-HCC malignancies is clinically effective. Therefore, the item or service is considered experimental, and, thus, is not reasonable and necessary, for the treatment or diagnosis of the illness or injury or to improve the functioning of a malformed body member in the population(s) specified in the request for national coverage. Therefore, we intend to continue national noncoverage of liver transplantation for malignancies other than HCC.

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Decision Memo

To: Administrative File CAG: 00101N
Liver Transplantation for Patients with Malignancies

From:

Sean R. Tunis, MD, MSc
Director, Coverage and Analysis Group

Steve Phurrough, MD, MPA
Director, Division of Medical and Surgical Services

Madeline Ulrich, MD, MS
Medical Officer

Jackie Sheridan-Moore
Technical Advisor

Samantha Richardson
Health Insurance Specialist

Peter Houck, MD
Medical Officer, Region X

Subject: National Coverage Decision
Date: April 30, 2002

This memo serves four purposes: (1) outlines clinical background on non-hepatocellular (non-HCC) malignancies and current treatment options; (2) reviews the history of Medicare's coverage of liver transplantation; (3) presents and analyzes the relevant scientific and clinical data related to liver transplantation for malignancies other than hepatocellular carcinoma (HCC); (4) delineates the reasons for continuing Medicare non-coverage of liver transplantation for malignancies other than HCC.

Clinical Background

Orthotopic liver transplantation (in situ replacement of a recipient's liver with a donor liver) has become the definitive therapy for patients with end stage liver disease due to a variety of causes. However, its role in the treatment of patients with preexisting malignancies is controversial. Included in this group are patients with primary and metastatic liver tumors, and those with a known history of extrahepatic malignancies. A number of studies have suggested that the high risk of tumor recurrence (due to residual disease and the effects of immunosuppression) in these patients may not justify orthotopic liver transplantation (OLT). On the other hand, despite its many potential short and long-term complications, OLT may offer the only chance of cure for some patients while providing meaningful palliation for others. Nonetheless, few transplant centers currently offer liver transplantation to patients with known hepatic malignancies other than hepatocellular carcinoma.

As of December 2001, the Scientific Registry of Transplant Recipients (SRTR) database, which contains information on almost every cadaveric transplant performed in the United States, included 37,357 liver transplants performed between 1990 and 2001. Of these 37,357 transplants, 889 patients had a malignancy at the time of transplant, including 273 in which a malignancy other than HCC was described as the primary reason for transplantation. One hundred twelve transplants were performed for bile duct tumors, 59 for neuroendocrine tumors, 66 for mesenchymal tumors, 4 for metastatic disease, and 32 for other non-HCC tumors.

There are a number of different non-HCC malignancies for which liver transplantation may be considered as treatment. The most common is primary cholangiocarcinoma. Primary cholangiocarcinoma, a rare malignant mucin-producing adenocarcinoma arising from the billiary epithelium often associated with pre-existing primary sclerosing cholangitis, accounts for 10-15% of all hepatobiliary tumors in the US.[1] Average 5-year survival is approximately 5-10 percent. Surgery offers the only possibility of a cure. Curative resection without transplantation has typically been seen only in early stage disease in patients who have no detectable affected lymph nodes or distant liver metastases; absence of vascular invasion; and no disseminated disease or involvement of adjacent organs. As a general rule, patients who have been offered liver transplantation have not been candidates for other potentially curative surgical procedures.

Neuroendocrine tumors are uncommon tumors that are capable of secreting peptide hormones into the circulation, which can result in a variety of clinical signs and symptoms. The most common neuroendocrine tumor causing liver metastases is carcinoid.[2] Metastatic disease in the liver is rarely solitary and only a small number of patients have lesions that are sufficiently localized to allow curative resection. Neuroendocrine tumors tend to recur, and in some patients metastases may develop many years after resection of the primary tumor. Principal treatment options include medical therapy aimed at reducing tumor size and inhibiting hormone secretion, and invasive methods such as intra-arterial infusion of cytotoxic drugs, hepatic artery embolization, or irradiation and surgical resection or transplantation.

Hepatic epithelioid hemangioendothelioma is a rare, low-grade malignant neoplasm of vascular origin. Presenting complaints include abdominal discomfort/pain, weight loss, weakness and fatigue. Because hepatic epithelioid hemangioendothelioma has an unpredictable course and prognosis, treatment modalitities are not standardized. Partial hepatectomy, chemotherapy, and radiotherapy have all been used. The wide variability in natural history of the disease limits assessment of treatment efficacy. Twenty percent of patients die within the first 2 years after presentation, whereas 20 percent have extended survival for 5 to 28 years, irrespective of treatment.[3]

Soft tissue tumors are classified according to which mesenchymal tissue they most closely resemble histologically. The natural history of soft tissue sarcomas and hepatic metastases from soft tissue tumors has not been described well, in part due to extensive heterogeneity of tumor types. Median survival after diagnosis of hepatic metastases has been described to be 12 months, and 5-year survival is uncommon.[4] Chemotherapy has not been shown to have a substantial impact on survival. Resection of isolated liver metastases has not been reported to improve survival, primarily because of limited surgical options that can successfully treat multicentric and bilobar lesions at the time of diagnosis.

Metastatic tumors are the most common malignant neoplasm of the liver in the U.S. The most frequent tumors to metastasize to the liver include those originating in the gastrointestinal tract, lung, and breast. Other solid tumors that metastasize to the liver include bladder cancer, neuroendocrine tumors, melanoma, and renal cell carcinoma. Prognosis is poor once tumor metastases have occurred, with a mean survival after diagnosis of 6 months. Selected patients may be surgical candidates for resection of isolated metastases, particularly those from colorectal adenocarcinoma, if the primary tumor has been removed and spread is confined to the liver. Less invasive methods of treatment, such as ethanol injection, cryotherapy, and laser vaporization are currently under evaluation. The 5-year survival following liver resection for colorectal metastasis is reported to be 25-37 percent.[5]

Gallbladder carcinoma is the fifth most common gastrointestinal malignancy. It occurs more commonly in women and peaks in incidence during the seventh decade of life.[6] Over 89 percent of gallbladder carcinomas are adenocarcinomas, with the remaining cases being adenosquamous carcinoma. Advanced local and regional disease usually is present at the time of diagnosis. Prognosis and outcome of gallbladder cancer is usually poor. Median survival is 11 months or less despite therapeutic intervention.[7] The principal treatment for gallbladder cancer is the removal of the primary tumor and the areas of local extensions. Chemotherapy, external beam radiation, and intra-arterial chemotherapy have also been used, but at best, response rates are 10-20 percent. Complete remission is rare.

Liver transplantation in patients with a preexisting extrahepatic malignancy is thought to pose special problems. Because of the long-term immunosuppression that accompanies liver transplantation, there is increased concern about the risk for recurrent or de novo tumors as well as accelerated tumor growth. For these reasons, the presence of preexisting malignancy is often considered a relative contraindication to liver transplantation. However, available alternative treatments for end-stage liver disease in the setting of preexisting malignancy are limited, and depend on the etiology of the underlying liver disease process.

The published literature also describes assorted rare liver malignancies that have occasionally been treated by liver transplantation. Tumors include primary liver lymphoma, hemangiopericytoma, liver adenomatosis, lymphangioma, cystadenocarcinoma, and Caroli's disease with unresectable adenocarcinoma of the intrahepatic bile ducts. For purposes of this analysis and the technology assessment report, these rare tumors have been looked at as a group.

History of Medicare's Coverage of Liver Transplantation

Medicare first issued a national coverage policy on liver transplantation in 1984. This initial policy limited coverage of liver transplantation to pediatric patients (under age 18) with extrahepatic biliary atresia or any other form of end-stage liver disease, except that coverage was not provided for children with a malignancy extending beyond the margins of the liver or those with persistent viremia. Following review of an August 14, 1989, technology assessment report prepared by the Office of Health Technology Assessment in the Public Health Service, The Centers for Medicare and Medicaid Services (CMS formerly called HCFA) published a notice in the Federal Register (56 FR 15006) on April 12, 1991 expanding Medicare coverage of liver transplantation to adults with one of the following conditions: primary biliary cirrhosis; primary sclerosing cholangitis; postnecrotic cirrhosis due to hepatitis B surface antigen negative; alcoholic cirrhosis; alpha-1 antitrypsin deficiency disease; Wilson's disease; or primary hemochromatosis. In addition, CMS limited Medicare coverage to transplants performed in qualifying facilities.

The Federal Register Notice specified the criteria for approval of transplant centers to perform Medicare covered liver transplants. Criteria include the facility's patient selection policies, patient management protocols, commitment of resources to the transplant program, facility plans for continued performance, experience and survival rates, maintenance of data, and laboratory services. The patient selection standards for qualifying centers require the exclusion of patients with malignancies (56 FR 15006-7). However, these standards may be waived at the time of approval for centers that can demonstrate they maintain high quality liver transplantation results while using other standards. Medicare coverage is effective with the date of the transplant center's approval. The first approval for liver transplantation in adults was on March 8, 1990.

In June 1993, a committee of physicians from various Government agencies and Medicare contractor medical directors considered expanding the diagnoses for Medicare coverage of liver transplantation at the request of the University of Pittsburgh Medical Center. The committee recommended that CMS examine the current literature and solicit expert opinion to determine whether Medicare should change its current policy of covering liver transplantation for specific conditions to covering liver transplantation for patients with any form of end-stage liver disease, with certain exceptions. Malignancy was specifically noted as one of the exceptions contemplated.

CMS staff reviewed the medical literature and analyzed data from the Scientific Registry of Transplant Recipients (transplants performed in the United States). We also analyzed CMS's internal database that was generated from information submitted with applications from transplant centers applying for Medicare approval. The information showed that patients being transplanted for malignancies and hepatitis B had significantly worse long-term survival outcomes than patients transplanted for other end-stage liver diseases. Analysis of data from the institutions that applied to CMS to be approved for coverage of liver transplants showed 5-year survival among patients with malignancy was 33.6 percent, compared with 70 to 80 percent among patients with six of the seven non-malignant conditions initially covered by Medicare.[8] CMS determined that the literature supported expansion of coverage of transplants for end-stage liver disease, but not for malignancy. Effective July 15, 1996, Medicare coverage of liver transplantation was expanded to include all end-stage adult liver disease except hepatitis B or malignancies. The NCD was further expanded on December 10, 1999 to include coverage for individuals with hepatitis B. (See Coverage Issues Manual 35-53.)

More recently, CMS became aware of published studies showing that outcomes for patients undergoing transplant and having HCC may not be as poor as previously believed. We decided to internally generate a NCD request to determine whether new literature supported a change in our coverage policy. After analysis of the literature, we concluded that liver transplantation for patients with HCC could be covered under certain circumstances. The decision memorandum published at www.cms.hhs.gov/coverage/8b3-rr2.asp outlined that decision. Medicare currently covers liver transplantation for patients with HCC under the following circumstances:

- The patient is not a liver resection candidate;
- The patient's tumor(s) is less than or equal to 5 cm in diameter;
- There is no macrovascular involvement; and,
- There is no identifiable extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs or bone.

This decision was published in section 35-53 of the Coverage Issues Manual and became effective September 1, 2001.

At the time we issued a decision memorandum announcing our intention to publish a NCD for liver transplantation for patients with HCC, we also announced on the Internet our intention to review the evidence available regarding malignancies other than HCC. The public was invited to share their views regarding this topic and provide us with evidence that should be considered. We have not received any comment from the public or professional organizations related to liver transplantation for patients with malignancies other than HCC.

Summary of Evidence

CMS began its analysis of this issue with a search of the medical literature. It was clear from the survey of literature we conducted that there was a limited volume of literature available regarding liver transplantation for malignant disease other than HCC. We requested a technology assessment (TA) in May 2001 from the Agency for Healthcare Research and Quality (AHRQ)and AHRQ subsequently contracted with New England Medical Center to perform the assessment. The final report was presented to the CMS on February 20, 2002. (See http://www.cms.hhs.gov/coverage/download/8b3-xx.pdf.) The summary of evidence below is from the TA.

The primary source of evidence for the TA was the published literature and registry data from the SRTR. The published literature regarding transplantation in the setting of malignancy was identified by AHRQ by performing a search of the MEDLINE® database. The search was restricted to articles published in English between January 1990 and July 2001. The final list of search terms was derived after consultation with hepatologists, oncologists and from terms identified from review articles. Search terms included: neoplasms, tumor$, canc$, carcin$, neoplas$, metasta$, malignan$, liver transplantation, liver transplant$, hepat$ transplant$[9], cholangiocarcinoma, hemangioendothelioma, hemangiosarcoma, leiomyosarcoma, lymphoma, neuroendocrine, apudoma, islet cell.

Studies were included that described any outcomes following liver transplantation in adult patients (age >18) with primary or metastatic liver tumors (other than hepatocellular carcinoma), or in patients with a history of prior extrahepatic malignancy. Studies were excluded if they presented outcomes following liver transplantation that could not be differentiated from outcomes following other types of therapeutic interventions, described transplantation for a non-malignant tumor or premalignant state (e.g., biliary papillomatosis), included only patients with concurrent hepatocellular carcinoma, presented outcomes following liver transplantation that were not distinguishable for individual tumors, presented only de novo cancers following liver transplantation, included tumors in the donor or donor graft, reviewed other sources of primary patient data or represented duplicate reports of previously-described patients.

Titles and abstracts were reviewed to identify relevant articles. The bibliographies from review articles and from reports that fulfilled the inclusion criteria were examined to identify other potentially relevant studies. All studies were reviewed in duplicate to determine which studies should be included in the evidence report based upon the inclusion and exclusion criteria described above.

The TA report looked at results for cholangiocarcinoma, neuroendocrine tumors epithelioid hemangioendothelioma, soft tissue sarcoma, metastatic tumors, gallbladder cancer, preexisting extrahepatic malignancy, and transplantation for other tumors. Below are the findings for each category of malignancies.

A. Cholangiocarcinoma. One hundred seven transplants have been performed in the United States since 1990 for cholangiocarcinoma. The TA report reviewed 49 reports of liver transplantation for cholangiocarcinoma from 28 transplant centers describing outcomes for 693 patients undergoing OLT or extended procedures. All studies were individual case reports, or case series. Eighteen included at least 10 patients (total 555 patients). Studies varied widely regarding length of follow-up and details of reported outcomes. Nevertheless, after reviewing the available data the technology assessment reported the following general conclusions:

- Median patient survival was 11.8 months when combining all studies that included a minimum of 10 patients. Overall 1-, 3-, and 5-year patient survival was 63%, 46%, and 22%, respectively. For comparison, 1-, 3-, and 5-year patient survival following liver transplantation for chronic hepatitis C is 79, 79, and 66, respectively, and 1-, 5 -, and 7-year patient survival following transplantation for alcoholic liver disease is 84, 72, and 63%, respectively.

- Recurrence was reported in 52% of patients when combining all studies that included a minimum of 10 patients (total 543 patients). The mean follow-up was 53 months. Overall 1-, 3-, and 5-year disease-free survival in all patients was 58%, 22%, and 13%, respectively.
- Graft survival was reported in two studies including a minimum of 10 patients. One-year graft survival was 92% in 24 patients.
- There were insufficient data describing quality of life following OLT for cholangiocarcinoma to make general conclusions.
- There were insufficient data to make firm conclusions regarding patient, tumor, or transplant characteristics that were associated with a favorable prognosis. However, limited data suggested that one-year patient survival was better in patients with tumors diagnosed incidentally compared to those in whom it was diagnosed preoperatively. In addition, prognosis appeared to be better in patients with negative lymph nodes and no residual disease after surgery.
- Adjuvant and neoadjuvant chemotherapy did not appear to improve survival.
- Patient and disease-free survival did not appear to improve during the last decade.

B. Neuroendocrine Tumors Fifty-eight transplants have been performed in the United States since 1990 for neuroendocrine tumors. AHRQ's search revealed 26 reports of liver transplantation for neuroendocrine tumors from 22 transplant centers describing outcomes for 129 patients. All studies were individual case reports or case series. Five included at least 10 patients (total 81 patients). Studies varied widely regarding length of follow-up and details of reported outcomes. Nevertheless, after reviewing the available data the TA reported the following general conclusions:

- Median patient survival was 30.7 months when combining all studies that included a minimum of 10 patients (total 81 patients). Overall 1-, 3-, and 5-year patient survival was 64%, 60%, and 53%, respectively.
- Recurrence was reported in 52% of patients when combining all studies that included a minimum of 10 patients (total 81 patients). Not enough details are provided to estimate 1-, 3-, and 5-year disease-free survival following OLT for neuroendocrine tumors.
- Graft survival was reported in four reports including a total of 17 patients. None of these reports included a minimum of 10 patients. Six patients experienced graft failure.
- Fourteen reports included details describing quality of life following OLT for neuroendocrine tumors. Two studies included a minimum of 10 patients (total 21 patients). Periods of symptom-free survival following OLT ranged from 5 to 106 months. Studies with longer follow-up periods demonstrated palliation of clinical symptoms, although most patients were still affected by tumor recurrence.
- There were insufficient data to make firm conclusions regarding patient, tumor, or transplant characteristics that were associated with a favorable prognosis.
- There were insufficient data to make conclusions regarding affect of adjuvant and neoadjuvant therapies, or extended transplantation, or prognosis following OLT.

C. Epithelioid Hemangioendothelioma. At least 66 liver transplants have been performed in the United States since 1990 for soft tissue tumors. Forty-five of these transplants were performed for "hemangioendothelioma-hemangiosarcoma." AHRQ's search revealed 15 reports of liver transplantation for soft tissue tumors. Eight reports from seven transplant centers describe outcomes for 42 patients with hepatic epithelioid hemangioendothelioma. All studies were individual case reports or case series. Only one study included a minimum of 10 patients (total 16 patients). Studies varied widely regarding length of follow-up and details of reported outcomes. Nevertheless, after reviewing the available data the TA reported the following general conclusions:

- Median survival ranged from 9 to 65 months. The largest study did not report median survival. Overall 1-, 3-, and 5-year survival rates were 100%, 85.7%, and 71.3%, respectively.
- Recurrence was reported in 55% of patients in the largest series (total 16 patients) with a median follow-up of 52 months. One, 3-, and 5-year disease-free survival was 81.3%, 68.6%, and 60.2%, respectively.
- Graft survival was reported in one study that included a minimum of 10 patients. Three of 16 patients required retransplantation at 2 days, 4 days, and 4 years.

- Two reports included details describing quality of life following OLT. One patient was alive with residual, “asymptomatic” disease 32 months following OLT. Two additional patients had “normal quality of life” at 9 month and 44 month follow-ups.
- There were insufficient data to make firm conclusions regarding patient, tumor, or transplant characteristics that were associated with a favorable prognosis.

D. Soft Tissue Sarcoma. Ten reports from six transplant centers provided outcomes for 20 patients following OLT for soft tissue tumors other than hemangioendothelioma. All studies were individual case reports or case series. None of the studies included a minimum of 10 patients. Studies varied widely regarding length of follow-up and details of reported outcomes. Given these limitations, the authors of the TA believe the available data support the following general conclusions:

- Mean patient survival ranged from 2.5 to 24 months for all 19 reported patients. Overall 1-, 3-, and 5-year patient survival was 100%, 44%, and 44%, respectively, in the largest series (total 6 patients).
- Recurrence ranged from 50 to 100% in all reports. The largest series reported recurrence in 83% of patients.
- Graft survival was not reported in any study describing outcomes following OLT for soft tissue tumors other than hemangioendothelioma.
- One report included details describing quality of life following OLT for soft tissue tumors other than hemangioendothelioma. Two patients were reported to be “alive” without early satiety or pain with meals 12 and 15 months following OLT.
- There was insufficient data to make firm conclusions regarding patient, tumor, or transplant characteristics that were associated with a favorable prognosis.

E. Metastatic Tumors. The exact number of liver transplantations performed in the United States for metastatic tumors is unclear. At least three transplants have been reported for “Meta Disease – lung ca”, “metastatic carcinoma”, and “sigmoid carcinoma 12/89.” AHRQ’s search revealed 7 reports of liver transplantation for metastatic disease from 4 transplant centers describing outcomes for 26 patients. All studies were individual case reports or case series. One study included 10 patients. Studies varied widely regarding length of follow-up and details of reported outcomes. Nevertheless, after reviewing the available data the TA reported the following general conclusions:

- Median patient survival ranged from 5 to 31 months. The study that included 10 patients reported no survivors beyond 3 years.
- Recurrence was reported in 75 to 100 percent of patients. Mean time to tumor related mortality was 8.3 months. Time to tumor related death in all studies ranged from 2 weeks to 31 months.
- Graft survival was reported in one study of eight patients. Two patients experienced recurrence of lymphoma in the allograft at 2 weeks and 2 months following OLT.
- Quality of life following OLT for metastatic disease was not addressed in any report.
- There were insufficient data to make firm conclusions regarding patient, tumor, or transplant characteristics that were associated with a favorable prognosis.

F. Gallbladder Cancer. Two transplants have been performed in the United States since 1990 for gallbladder cancer. AHRQ’s search revealed a total of four patients with gallbladder cancer reported from 3 transplant centers. All four patients were discussed in three individual case series. Thus, the TA reported no general conclusions for this indication.

G.Preexisting Extrahepatic Malignancies. The number of liver transplants performed in the United States since 1990 for patients with preexisting extrahepatic malignancy is not known because the Organ Procurement and Transplantation Network (OPTN) only recently began inquiring about previous malignancy. AHRQ's search revealed 11 reports of liver transplantation from 11 transplant centers describing outcomes for 76 patients with preexisting extrahepatic malignancy. All studies were individual case reports or case series. Two studies included a minimum of 10 patients (total 62 patients). Studies varied widely regarding etiology of liver disease, location of previous malignancy, length of follow-up, and details of reported outcomes. Nevertheless, after reviewing the available data the TA reported the following general conclusions:

- Median patient survival ranged from 24 to 102 months. The largest series reported that 81 percent of cancer related deaths occurred within 2 years.
- Recurrence or persistence of a preexisting malignancy was described in 24 percent of patients with a median follow-up of 7.5 months (range 1.5 to 42.5 months)(total of 44 patients). These preexisting malignancies had been treated 6.5 to 41 months prior to OLT.
- Graft survival was reported in one study. One of six patients required regrafting at 6 months.
- Five reports include details describing quality of life following OLT. All reports described patients as "alive and well" or "well". One patient returned to pre-bone marrow transplant weight, one returned to "baseline functional status", and one returned to "100 percent performance status". One patient who required mechanical ventilation during almost the entire post-operative period had reported "improved mental status" prior to death.
- There were insufficient data to make firm conclusions regarding patient, tumor, adjuvant or neoadjuvant chemotherapy, or transplant characteristics that were associated with a favorable prognosis.

H. Transplantation for Other Tumors. Seven liver transplants for lymphoma and 15 liver transplants for secondary hepatic malignancies have been performed in the United States since 1990. AHRQ's search revealed six reports of liver transplantation for other tumors from five transplant centers describing outcomes for 6 patients. All studies were individual case reports or case series. The heterogeneity of the described patients limited the authors of the TA in formulating general conclusions.

Transplant Registry

The technology assessment report also used information from the OPTN to provide an estimate of the frequency with which liver transplantation has been performed in the setting of malignancy in the United States during the last decade.[10] In accordance with OPTN requirements, transplant centers report diagnostic information on patients at the time of listing for transplant, at the time of transplant, and at regular follow-up intervals after transplantation. Data collected include the recipient's primary liver disease and the presence of known malignancies at the time of listing. These data are stored int eh SRTR database.

Despite an increase in the total number of liver transplants performed annually (from 2177 in 1990 to 4,384 in 2000), the number of transplants performed for tumors other than HCC declined. In 1990, 52 recipients underwent OLT for non-HCC tumors compared to13 in 2000. An average of 20 transplants was performed each year for the last five years, while an average of 32 transplants was performed each year from 1990-1995. The decrease was largely due to a reduction in the number of transplants being performed for patients with cholangiocarcinoma. Of the 75 transplants performed for cholangiocarcinoma in the last 10 years, 17 occurred in 1990, 13 in 1993, 8 in 1996, 7 in 1999, and 4 in 2000. A similar decrease has been observed for patients with leiomyosarcomas; 14 patients with leiomyosarcoma underwent OLT from 1990 to 1995 compared to only one from 1996 to 2000. Transplantation for hemangioendotheliomas has remained relatively stable with an average of four OLT performed each year. In contrast, twice as many transplants were performed each year for neuroendocrine tumors in the early 1990s compared to the last 5 years.

Of over 200 living donor liver transplants to adult recipients performed in the United States between 1997 and 2001 and reported to the OPTN, nine have been to recipients with non-HCC tumors. Three recipients were diagnosed with hemangioendothelioma, two with primary liver malignancy not otherwise specified, and one each with: cholangiocarcinoma, neuroendocrine tumor, spindle cell tumor, secondary liver malignancy not otherwise specified, and leiomyosarcoma.

The OPTN is responsible for allocating organs to patients on the transplant waiting list. Livers are allocated to patients by blood type, severity of illness, and time on waiting list within geographical areas. Patients with hepatocellular carcinoma that are good transplant candidates because of the tumor size and stage are classified into a high severity class based on the disease in an effort to transplant them early. The OPTN does not have a policy to give preferential treatment to other malignancies for adult patients. These patients are considered the same as any other transplant candidate and malignancy has no effect on their priority.

CMS Analysis

We have conducted a literature search and independently reviewed the literature that was reviewed in the preparation of the technology assessment report as part of analysis of this issue as discussed below. In addressing the issue of Medicare coverage for liver transplantation for patients with malignancies other than HCC, the following questions arise:

1. Does enough information exist about liver transplantation for patients with malignancies other than HCC for CMS to determine that basic safety and efficacy issues have been resolved?

The technology assessment uncovered 110 reports that met the inclusion criteria. Forty-nine transplant centers published results that included a total of 1,011 transplant recipients. The largest experience was with cholangiocarcinoma and neuroendocrine tumors (total 822 patients). All of the reports were individual case reports or case series. None of the studies performed comparative analyses with other treatment alternatives for the disease or with transplants for other diagnoses. While some centers reported on both resection and transplantations for the same type of malignancy in the same study, none drew conclusions as to when one modality resulted in a better patient outcome. Details regarding the patient and tumor characteristics; immunosuppression; patient, disease-free and graft survival; and quality of life were reported with variable detail.

It is not possible to make a reliable assessment of clinical effectiveness from single case reports or very small case series. That is, we can not form general conclusions about the health care benefits and risks associated with an item or service to the Medicare population from the results of a single beneficiary or a small group of beneficiaries as we have no basis to believe that all beneficiaries would react similarly to that single individual or small group. We were not able to locate any scientific report of patient survival containing 10 or more patients for gallbladder cancer or soft tissue tumors other than hemangioendothelioma. Further, despite the fact that metastatic tumors are the most common malignant neoplasms of the liver, we found only one study that had at least 10 cases of patients receiving liver transplantation for cancer metastasizing to the liver. Similarly we found one study of 16 cases of patients receiving liver transplantation for epithelioid hemangioendothelioma. In looking at data for liver transplantation within the United States from the SRTR, we find that these transplants are extremely rare and not likely to occur in Medicare beneficiaries. That is, the SRTR reports only two cases of liver transplantation for gallbladder cancer, and one case of epithelioid hemangioendothelioma. Therefore, CMS determines that the evidence is not adequate to conclude that liver transplantation in patients with gallbladder cancer, soft tissue tumors other than hemangioendothelioma, metastatic disease to the liver, and epithelioid hemangioendothelioma is clinically effective. In the absence of evidence, the item or service is considered experimental, and, thus, is not reasonable and necessary, for the treatment or diagnosis of the illness or injury or to improve the functioning of a malformed body member in the population(s) specified in the request for national coverage.

There were two case series involving a total of 62 patients related to preexisting extrahepatic malignancy. These case series, however, do not include information regarding patient, graft, or disease-free survival or operative mortality. Without information regarding survival, CMS determines that the evidence is not adequate to conclude that liver transplantation for patients with preexisting extrahepatic malignancies is clinically effective. Therefore, the item or service is considered experimental, and, thus, is not reasonable and necessary, for the treatment or diagnosis of the illness or injury or to improve the functioning of a malformed body member in the population(s) specified in the request for national coverage.

There were five case series that included at least 10 patients transplanted to treat neuroendocrine tumors. These five studies included a total of 81 patients. They showed 15 percent operative mortality, and 1-3-and 5- year patient survival of 64, 60 and 53 percent. None of the studies include details of the stage of disease, disease-free survival, or graft survival. There were 18 liver transplants for neuroendocrine tumors in the SRTR. CMS determines that the evidence is not adequate to conclude that liver transplantation for patients with neuroendocrine tumors is clinically effective. Therefore, the item or service is considered experimental, and, thus, is not reasonable and necessary, for the treatment or diagnosis of the illness or injury or to improve the functioning of a malformed body member in the population(s) specified in the request for national coverage.

Several studies of cholangiocarcinoma attempted to identify prognostic factors that might lead to decreased tumor recurrence and subsequent decreases in resulting mortality. Complete resection of early disease seems to offer the best chance of long term cure. Early disease is difficult to diagnose, however, particularly in the setting of primary sclerosing cholangitis, a known risk factor, which obstructs the normal structure of the biliary tree. By the time a tumor is recognized it is frequently likely spread beyond the liver. Further, pre-existing inflammation and subsequent scarring make accurate pre-operative staging via imaging more difficult. Extended procedures and cluster transplantations have not lead to increased survival among patients who continue to have high levels of recurrence and mortality. Serum tumor markers, such as CEA and CA 19-9 may be elevated, but are not specific for disease. Development of better methods of early detection and assessment of pre-operative tumor burden and extent may improve long term survivorship.

Most of the information related to liver transplantation for malignancies other than HCC is related to patients with cholangiocarcinoma. There were 15 case series with more than 10 patients that reported on patient survival and 18 studies that reported on disease-free survival. Some of the studies reported on disease staging, but did not calculate separate survival statistics by stage. The operative mortality was 14 percent, recurrence rate was 52 percent, and median patient survival was 11.8 months. 1-3-and 5- year patient survival was 63, 46 and 22 percent respectively. Disease-free survival at 1-3- and 5- years was 58, 22 and 13 percent.

We believe that there is enough information about liver transplantation for patients with cholangiocarcinoma and neuroendocrine tumors to allow us to further evaluate these topics.

2. Are the study designs sufficient to answer the clinical questions pertinent to Medicare beneficiaries?

None of the studies were randomized or prospective design. However, we recognize that, given the nature of transplantation as a life saving technology and the shortage of organs necessitating a strict national allocation mechanism, conduct of prospective or randomized trials for liver transplantation of malignancies would be extremely difficult, if not impossible.

Further, none of the studies utilized any comparison cohorts. Comparison cohort studies are possible for liver transplantation for malignancies as evidenced by the literature we analyzed in making our determination regarding hepatocellualar carcinoma. While we acknowledge that there are fewer patients with non-HCC malignancies receiving transplants than with HCC, comparison cohort design studies are needed to properly evaluate transplantation in these patient groups.

The studies that are available are all, with one exception, small case series. Many of the studies include less than 20 patients. In most, there is no indication how the study participants were selected, so it is difficult to analyze selection biases in the studies. It is possible that patients were included in more than one published study.

Details regarding length of follow-up, tumor staging, tumor size or other variables associated with prognosis following transplant were included sporadically. Thus, unlike the HCC data, we were not able to identify patient characteristics that might explain increased likelihood of success. In conclusion, CMS determines that the studies reported to date are not adequate to conclude that liver transplantation for patients with malignancies other than HCC is clinically effective. Therefore, the item or service is considered experimental, and, thus, is not reasonable and necessary, for the treatment or diagnosis of the illness or injury or to improve the functioning of a malformed body member in the population(s) specified in the request for national coverage.

3. How does the survival of patients with non-HCC malignancies compare to other Medicare covered indications for liver transplantation?

Despite the fact that study results suffer from significant analytical deficiencies, it is useful to make comparisons between the best estimates of the outcomes of liver transplantation for non-HCC malignancies and other indications for liver transplantation.

Overall, 1-, 3-, and 5-year patient survival for patients with cholangiocarcinoma from the studies was 63 percent, 46 percent and 22 percent respectively. Similarly, overall survival from the studies for neuroendocrine tumors was 64 percent, 60 percent and 53 percent. We compared this to data from the SRTR for 1-, 3-, and 5-year patient survival for patients transplanted for non-malignant disease of 84 percent, 78 percent and 73 percent.

The SRTR does not calculate HCC specific survival. Thus, we looked to some of the literature we used in making the determination to cover liver transplantation for HCC under Medicare. In Figueras' study of HCC transplant patients in 1990 through 1995, he calculated 1-, 3-, and 5-year patient survival of 84 percent, 74 percent and 60 percent.[11] Yamamoto similarly calculated 1-, 3-, and 5-year patient survival for 307 HCC transplant patients between 1981 and 1997 at 76 percent, 63 percent and 55 percent.[12]

A chart of the survival comparisons is as follows:

Group	1-year survival	3-year survival	5-year survival	Recurrence Rate
Cholangiocarcinoma	63%	46%	22%	52%
Neuroendocrine tumors	64%	60%	53%	52%

Group	1-year survival	3-year survival	5-year survival	Recurrence Rate
SRTR Overall	84%	78%	73%	
HCC Figueras	84%	74%	60%	7%
HCC Yamamoto	76%	63%	55%	20%

Thus, the outcomes for patients receiving transplants for cholangiocarcioma are much worse than for HCC or non-malignant transplants. Likewise, 1-year patient survival for neuroendocrine tumors is much lower than non-malignant or HCC transplants. However, the 3- and 5-year patient survival numbers from the studies on neuroendocrine tumor transplants are more similar to those for HCC transplants, especially the results from Yamamoto. Due to the lack of comparison studies, we are not able to determine the statistical significance of these differences in survival.

One of the important issues to consider in a determination related to liver transplantation for any malignancy is recurrence rate. Given the national shortage of organs and the number of people who die annually on the list awaiting a transplant, it is important to make NCDs regarding allocations of these scarce organs to persons that are most likely to be cured or at least attain long-term disease-free state following transplantation. The recurrence rate for both cholangiocarcinoma and neuroendocrine tumor is 52 percent. Figueras found HCC recurrence rate at 60 months of only 7 percent. Yamamoto found a recurrence rate of 20 percent. Thus, the recurrence rate for both cholangiocarcinoma and neuroendocrine tumors is much higher than that found in HCC patients transplanted. With the limited number of organs available, that higher rate is a strongly negative factor in considering extension of Medicare coverage.

4. Is liver transplantation as effective as other treatment options for non-HCC malignancies?

Given the limitations of the studies included in this assessment, we are not able to make comparisons between the effectiveness of liver transplantation and other treatment options for non-HCC malignancies. All of these malignancies are life threatening. Generally, patients are selected for transplantation only if other surgical treatment options, such as resection, are not possible, which is generally the case with advanced disease. However, there are no studies comparing outcomes between resection and transplantation as there are with HCC. Further, there are no studies comparing outcomes between transplantation and other non-curative therapies, such as chemotherapy.

Supporters of transplantation for these malignant diseases argue that transplant is the only possibility of cure for patients who are not candidates for resection. They believe that patients should have this option available to them. However, we note that transplantation is not without risk. The overall operative mortality associated with transplantation in the referenced studies was approximately 15 percent.

Conclusion

In summary, after studying the technology assessment report prepared by AHRQ, reviewing much of the literature independently and discussing the issue with noted leaders in the transplant community in the U.S., we find that:

(1) available evidence does not indicate that liver transplantation for malignancies other than HCC produces outcomes that are comparable to those achieved with other liver transplants;

(2) there are no cohort studies comparing liver transplantation to other treatment options for any non-HCC malignancy; and

(3) most of the available literature is individual case studies or very small case series and is not adequate to make a positive coverage determination.

Nonetheless, we evaluated the information provided in the studies and found that:

(1) the information suggests that liver transplantation for non-HCC malignancy produces outcomes statistics in terms of mortality that are substantially lower than transplantation for other diagnoses;

(2) the transplants do not appear to be curative in the majority of the cases since in over half of recipients the disease recurs;

(3) there has been a significant decline in the number of transplants performed for non-HCC malignant disease in the U.S.

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act. (Section 1869(f)(1)(B).) In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within part A or part B, and must not be otherwise excluded from coverage. (In this case, liver transplantation falls within the inpatient hospital and physician services benefit categories.) Moreover, in general, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. (section 1862(a)(1)(A).)

As described in this decision memorandum, we have fully examined the medical and scientific evidence submitted with the request for a national coverage decision. CMS determines that the evidence is not adequate to conclude that liver transplantation in patients with non-HCC malignancies is clinically effective. Therefore, the item or service is considered experimental, and, thus, is not reasonable and necessary, for the treatment or diagnosis of the illness or injury or to improve the functioning of a malformed body member in the population(s) specified in the request for national coverage. Therefore, we intend to continue national noncoverage of liver transplantation for malignancies other than HCC.

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1 de Groen 1999

2 Proye 2001

3 Ishak 1984

4 Jaques 1995

5 McCarter 2000

6 Piehler 1978

7 Bartlett 2000

8 Kilpe VE, et al. 1993

9 $ terminology in Medline searches for derivatives of the word. For example, neoplas$ would search for neoplasm, neoplasms, neoplastic, etc.

10 Section 372 of the Public Health Service Act established the Organ Procurement and Transplantation Network (OPTN). The Secretary of Health and Human Services is required to contract for the establishment and operation of the OPTN to establish a national list of individuals in need of organ transplants and a national system to match available organs to those in need. The OPTN develops criteria for allocating organs, assists in the distribution of organs, adopts standards for quality, coordinates transportation of organs, and disseminates information about organ donation and transplants.

11 Figueras 2000

12 Yamamoto J. 1999

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